Dr. Rajesh Doss

Deuterated Drugs –A New Beginning

An experienced synthetic organic chemist with over 18 years of experience in discovery, synthesis, process innovation & development. Actively involved in pre-clinical drug discovery services starting from hit identification to lead development. Expertise in characterisation and synthesis of nce`s, metabolites & impurities.

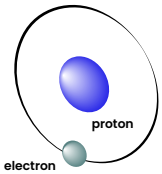
Introduction

Substitution of a Hydrogen Atom with its Heavy Isotope Deuterium (with one Additional Neutron) is known as Deuteration. This is often Utilised in Organic Chemistry to Probe Reaction Mechanisms, which now is finding a Promising Application in Drug Discovery.

Deuteration Prolong the Residence time of the Drug Species in Plasma to Achieve Greater Metabolic Stability, Reduced Toxicity, Increased Bioavailability and Efficacy[1]. Despite a Minimal Change, this led to the Successful Development of Deutetrabenazine, the first Deuterated Drug Approved by FDA in 2017[2]. Following this Success, many Deuterated Drugs are now being Evaluated and some of them are Already in Clinical Trials[3].

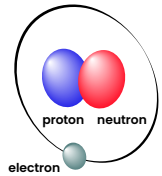
Hydrogen

^{1}H



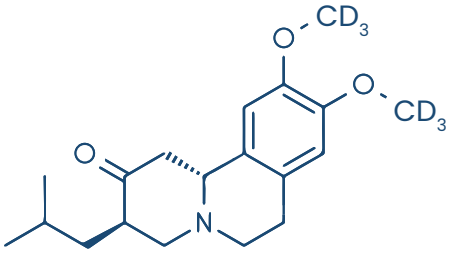
'Heavy' Hydrogen= Deuterium

$^{2}H=D$



Bond Strength

The Enhanced Activity after Deuterium Substitution can be Attributed to C-D Bonds being Stronger than C-H Bonds due to Higher Mass of Deuterium. It has Weaker Zero-Point Vibrational Energy **(ZPVE)** which Needs Higher Energy to Overcome the Barrier, which Otherwise is known as *Primary Kinetic Isotope Effect.* The **ZPVE** of C-D Bond is Tentatively Predicted to be around 0.74 times that of C-H Bond which Makes C-D Bond Stronger than C-H Bond.



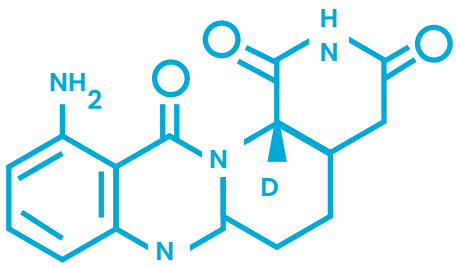
Deutetrabenazine

Reactions in which the C-H Bond is Broken During or Before the rate Determining step will be **slower** if the Hydrogen is Replaced by a Deuterium[4]. An Observable Isotope Effect will only be apparent, where the Breaking of a C-H or C-D bond is Involved in the Rate-Determining step or at the *"soft spot"* of a Molecule where it is Vulnerable for Bond Breaking.

For e.g., Deutetrabenazine, a Deuterium Substituted Tetrabenazine (a Vesicular Monoamine Transporter 2 **(VMAT)** in Hibitor) Supress Oxidative Metabolism of the Methoxy Groups which otherwise will lead to the Formation of Hydrotetrabenazine, a key Metabolite Associated with the Drug. This Metabolism Greatly Affects the Bioavailability of the Drug Leading to Increased Dosage.

Inhibition of Stereomutation

Another key Advantage of Deuterium Substitution is *stabilised enantiomerization* which is a Challenge while Designing a Drug Molecule. Avadomide is an oncology Drug which is known for its Rapid Interconversion between its Enantiomeric forms. A Deuterium Substitution at the Stereogenic centre slows down the Interconversion and Helps to Study the Enantiomers Independently for its efficacy without Racemization[5].



Deuterated Avadomide

Safety & Regulations

The Human Body Physiologically Contains about 15 mg/kg Deuterium[6], Mostly as D_2O. Laboratory Animals Remained Healthy in the Long Term Even when 25% of their Body Water (H_2O) Exchanged for Heavy Water (D_2O)[7].

The Approval of a Deuterated Analogue of a Drug may be Expedited via a 505(b)(2) Regulatory Pathway, where an Applicant can use the Data Sets of Studies Completed for Approval of the Parent Non-Deuterated Drug. However, due to Significantly Large KIE, FDA has Categorised Deutetrabenazine as a New Substance Rather than a Modified Tetrabenazine, allowing the Inventors to Patent the Same.

Deuterium Labelling @ JRF

JRF offers a Range of Deuterium Substituted Building Blocks (with Versatile Anchoring Groups) that can be easily Incorporated into any Drug Molecule During the Synthesis. We also offer Labelled Internal Standards and Markers. These Substituted Analogs Carry Excellent Isotopic Purity of 95 – 98%. We also offer Custom Synthesis of Building Blocks Tailored to an Individual Small Molecule.

Selected References :

1. Tung RD. Deuterium Medicinal Chemistry Comes of Age. Future Med Chem **2016**; 8(5):491-494.
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3. Rita Maria Concetta Di Martino, Brad D. Maxwell & Tracey Pirali Nature Reviews Drug Discovery **2023**, 22, 562–584.
4. Kopf S, Bourriquen F, Li W, Neumann H, Junge K and Beller M. Recent Developments for the Deuterium and Tritium Labelling of Organic Molecules. Chem Rev **2022**; 122(6):6634-6718.
5. DeWitt S, Czarnik AW, Jacques V. Deuterium-Enabled Chiral Switching (DECS) Yields Chirally Pure Drugs from Chemically Interconverting Racemates. ACS Med Chem Lett. **2020**, 5; 11(10):1789-1792.
6. Klein PD and Roseland Klein E. Stable Isotopes: Origins and Safety. The Journal of Clinical Pharmacology **1986**; 26(6):378-382.
7. Kushner DJ, Baker A and Dunstall TG. Pharmacological uses and Perspectives of Heavy Water and Deuterated compounds. Can J Physiol Pharmacol **1999**; 77(2):79-88.